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Via Sant 'Epifanio, 14
Pavia
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Dear Luca and Gio:

Further to our discussions on penicillin derivatives:

(1) As I should have known better, the natural penicillins are all amides of an organic acid with 6-aminopenicillanic acid; for example, benzylpenicillin is b-phenylacetamidopenicillanic acid. I will be interested to learn from you whether the corresponding amines, for example b-phenylethylaminopenicillanic acid are also biologically active.

(2) At any rate, your organic chemists should have no difficulty in suggesting ways of conjugating the miscellaneous components in a suitable fashion to aminopenicillanic acid. The obvious one that occurs to me is to treat the mixture with phosgene as a coupling agent which will give you a series of ureide derivatives, whose biological activity in general I do not know. The other approach is to form the mixed acid chlorides from the miscellaneous substrates by treatment with PCl_3 and then conjugate this with the 6-APA. These experiments should certainly be quite straight forward and I recommend they go ahead; meantime, let me know what you can about the potential activity of other types of substitution on 6-APA besides the amides.

(3) When I can, I will go back to the models to see what further approaches there might be to blocking the β-lactam linkage.

(4) I had a chance to check again with Seymour Hutner in New York and he confirmed that from their own work, there is indeed a very good correlation between the inhibition of the eighth nerve by streptomycin derivatives and their effect on the bleaching of Euglena - this might be worthwhile considering in the screening of streptomycin analogs. However, it would then be necessary to isolate different compounds from the mix and test them individually. It might be asking too much to hope for a compound that would both over-ride the resistance of the S^r mutation and also lack the eighth nerve effect.

(5) Hutner is also quite excited about the usefulness of a phagotrophic photosynthesizing protozoan, Ochromonas, as a screening agent. He thinks this behaves very much like animal cells do in very many regards. I do not know if

Hutner has any firm conflicting connections, but I think you might be well advised to talk to him if you have an occasion on your next trip.

Yours sincerely,

Joshua Lederberg
Professor of Genetics

P.S. (6) Tetracycline does have a number of reactive groups as we discussed. It might be worth doing at least a tentative for conjugating the mixed acyl chlorides with it and to look for an agent that would inhibit tetracycline resistant staphylococci. If the dimethylamino group at position four can be substituted by an amino, one might look at this as a plausible point of diverse substitution. And finally, one might try to do the same replacing the b-dichloroacetyl residue of chloramphenicol with the mixed acyl chloride substitution and searching for any antibiotic.

(7) The leading references to substitutive reagents in proteins are on the enclosed cards. In addition, I am sure that you will remember the references made by Freese at Princeton to hydroxylamine which he thinks attacks cytosine. His manuscript also refers to papers by Takemura and Staehlin as enclosed on the reactions of hydrazine and glyoxal respectively. I would of most of these reagents as preliminaries that would open up interesting molecules to further substitution.

(8) Apart from the fluoro and penicillin complexes, another group substitution reagent that might still be worth trying is paraaminobenzene-sulfonyl which might be expected to react with available amino groups through the sulfonylchloride and give rise to a new series of sulfonamate drugs. It is not obvious that the most effective compounds in this series have yet been discovered.

(9) It is quite possible that as the work goes on, you will be more embarrassed by having too many interesting compounds to test than too few. If this is the case, it may be advantageous to fractionate the starting material from some convenient technical standpoint such as solubility in various solvents. In this way you could at least assure yourself of the easiest separation of unreacted starting material.

(10) In addition to the reagents that we have talked about and which are summarized in the Reviews, we ought also to add periodate as an oxidizing agent that can open amino alcohol and glycol linkages and give rather reactive aldehyde groups. I think you will have enough to do with other aspects of the program but we ought to have a master list of reagents on hand for ultimate use.